REMARKS

Claims 32-54 were previously pending in this application. Claims 32, 38 and 42-44 are amended. No claims are cancelled. No new claims are added. Claims 49-54 are withdrawn. Claims 32-48 are pending for examination with claim 32 being an independent claim.

No new matter has been added.

Defective Oath or Declaration:

A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is enclosed. A new declaration signed by all of the inventors is enclosed herewith.

Double Patenting Rejection:

Claims 32-48 have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,635,624.

Applicants may file a Terminal Disclaimer depending on the claims that are found to be allowable. It is respectfully requested that the rejection be delayed until claims are found to be allowable.

Accordingly, withdrawal of the rejection of claims 32-48 is respectfully requested.

Claim Rejections – 35 USC §112:

Claims 23-48 have been rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method as claimed, wherein the vector comprises a gene encoding the hepatitis B virus surface antigen protein, and further wherein the vector comprises a promoter operably linked to the gene, such that the antigen is expressed in the subject, does not reasonably provided enablement for the use of a vector encoding any HBV antigen.

Initially Applicants have amended claim 32 to add the limitation that the vector includes a promoter for the expression of the hepatitis B virus antigen gene in the subject. The examiner had indicated that such language was important to the enablement of the claim.

The Examiner has examined several Wands factors to reach a conclusion of lack of enablement based on unpredictability of the invention and lack of guidance in the specification. Applicants disagree and address each of these specific points below.

The Examiner has cited two post-filing references to support a finding of unpredictability. For instance, the Examiner has stated "the state of the art of DNA vaccination is such that there are several significant limitations to the application of the same methodology in different species. Studies looking at the efficacy of DNA immunization using similar approaches in humans or large animals are 'not encouraging' since DNA vaccines are 'often less effective in large animals than in mice' (Babiuk et al., 2003)". Babiuk, however, proceeds to demonstrate efficient expression of antigens from vectors expressing HBV and BHV in cattle. Babiuk concludes that "various combinations of delivery systems can enhance immunity to DNA-based vaccines and make them practical for administration of these vaccines in large animals." Thus, Babiuk does not support the unpredictability of the invention. Babiuk actually demonstrates that with routine manipulation of parameters such as known delivery devices one of skill in the art can actually achieve good expression levels in large animals.

Rubanyi, published in 2001, is cited for the proposition that gene therapy is not predictable. For instance it is taught in Rubanyi that "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic." The teachings of Rubanyi are not relevant to the claimed invention. Rubanyi describes gene therapy which is a different technology than DNA vaccines, as is claimed in the current invention. For instance, Rubanyi teaches on page 116 first sentence in section 3.1 "The ultimate goal for gene therapy is the replacement, in a site-specific manner of a disease-causing gene with its 'healthy' counterpart." DNA vaccination does not involve replacement of missing or damaged body protein which must (i) be produced in the same cell type(s) where it would normally be produced, and (ii) then function as a normal protein. Additionally, site specificity for expression of the antigen does not change with different disease targets. The immune system is exposed to the expressed and presented antigen, so all DNA vaccines regardless of disease target can be expressed in the same cells or tissues. DNA vaccination involves expression of an antigen that can provoke an immune response, much like the

delivery of a protein antigen to the body. The enablement and technical hurdles of the two technologies are quite different. Thus, a reference such as Rubanyi which describes the unpredictability of gene therapy is not applicable to the predictability of DNA vaccine technology.

Further, in rebuttal to the Examiner's citation of post-filing references to demonstrate a lack of unpredictability, Applicants cite additional post-filing references that support the predictability of the invention as a whole as claimed. These references are summarized below.

The Kuhöber, et al reference, (J. Immunol 1996, v. 156, p. 3687-95) for instance, describes the use of DNA immunization to induce antibody and cytotoxic T cell responses to hepatitis B core antigen in mice. The authors found they could prime class I-restricted CTL responses to HBcAg in mice by DNA immunization (page 3693, column 1). Figure 2 illustrates the 4-week post-immunization serum Ab response of mice immunized with HBcAg particles, the plasmid DNA encoding HBcAg, or with control plasmids containing no DNA insert. In panel one, F and E demonstrate that the pCMV-1/c plasmid DNA encoding HBcAg results in a significantly higher antibody titer than did immunization with the pCMV-1 plasmid without the insert DNA. This reference demonstrates the use of hepatitis core protein in nucleic acid vaccines.

The Haynes, et al. reference (J. Biotech. 1996, v. 44, p. 37-42) also describes the use of DNA immunization to elicit antibody and cytotoxic T cell responses to hepatitis B in animals including pigs, mice, and rhesus monkeys. Results demonstrating the effectiveness of hepatitis B core antigen (HBcAg) in an expression vector in mice and rhesus monkeys are illustrated in Figure 2, which indicates the "moderate to strong HBcAg-specific endpoint IgG titers following the primary immunization and very strong titers following the booster immunization" (p.41, col.1). The immunizations were performed with "a vector encoding the hepatitis B core antigen (HBcAg) driven by the human CMV promoter" (p. 41, col. 1). A demonstration of the effectiveness of immunization with a hepatitis B surface antigen (HBsAg) vector is illustrated in Figure 1, which indicates that the immunizations resulted in HBsAg-specific serum antibodies in all animals tested and high protective levels of the antibodies in four of the five animals subjects. This reference indicates the effective use of hepatitis surface protein and core protein in nucleic acid vaccines.

It is concluded that given the unpredictability associated with DNA vaccination and gene therapy and the lack of guidance on specific antigens, it would have required undue experimentation for one of skill in the art to practice the claimed invention. As set forth above, applicants disagree that the standard of predictability of DNA vaccination and gene therapy is the same and that DNA vaccination is inherently unpredictable.

Applicants' teachings have enabled one of ordinary skill in the art to use any hepatitis antigen in the DNA vaccines. Prior to the instant invention, hepatitis B antigens were well known. The invention is based at least partly on the teaching of the invention that DNA vaccines can be used to achieve the same types of immunoprotective responses that had previously been observed with peptide antigens. This teaching is not limited to the surface proteins of hepatitis B but covers all antigens of hepatitis B virus. Since it was known prior to the invention that surface and core antigens and epitopes thereof are immunoprotective, the discovery according to the invention that DNA vaccines are effective at inducing local expression of a sufficient amount of hepatitis B viral antigens to produce an immunoprotective response applies generally to hepatitis B antigens.

According to the invention, DNA vaccines encoding for hepatitis B viral antigens and epitopes thereof are capable of producing an immunoprotective response. In support of this teaching, the specification has provided adequate guidance to one of ordinary skill in the art to make a DNA vector containing a gene for a hepatitis B viral antigen or epitope thereof, using standard recombinant DNA technology and methods for administering these DNA vaccines to a subject to achieve an effective and durable level of antibodies in the subject. Prior to the instant invention, hepatitis B protein antigens derived from the surface and core were both well known (e.g., US Patent 4,839,277 issued on June 13, 1989 which describes immunogenic hepatitis B core antigens; US Patent 4,803,164 issued on February 7, 1989 which describes hepatitis B surface antigens, each of which is cited in the attached Information Disclosure Statement). The gene sequences for these antigens were also well known (e.g., US Patent 4,710,463 issued on December 1, 1987 which describes recombinant DNA molecules capable of expressing HBV core and surface antigens). It was also well known at the time of the invention that epitopes can be immunogenic (e.g., US Patent 4,957,869 issued on September 18, 1990 which describes short peptide sequences that are

immunogenic). The combination of this known information with the teachings of the specification adequately enable the claimed invention.

It would not require undue experimentation for one of ordinary skill in the art to prepare the DNA vaccine which expresses hepatitis B antigens and to immunize a subject as described in the specification. Since the genes were known at the time of the invention for other hepatitis B viral antigens, it would have required only known recombinant biology techniques to generate plasmid vectors which were capable of expressing these antigens. Simple recombinant techniques for generating plasmids are well known in the art and are not considered to require undue experimentation.

Thus, the lack of guidance regarding specific antigens in the specification would not result in undue experimentation. There is no requirement that applicants list known structures in the specification that can easily be identified using publicly available search tools. At the time of the invention Applicants discovered that HBV antigens could be included in a plasmid vector and administered to animals to produce an antigen specific immune response. The technology discovered by Applicants is not limited by the choice of HBV antigen. Such antigens are known for producing an immune response against HBV. One of skill in the art would simply need to select the antigen of choice based on the publicly available information on HBV protein antigens. The corresponding DNA can be inserted into a vector, as taught by applicant and expressed in a subject to produce an antigen specific immune response. No undue experimentation is required.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

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Respectfully submitted,

By _____

Helen C. Lockhart
Registration No.: 39,248
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000